Pak. J. Chest Med. 2024;30(01)

Original Article

journal homepage: https:/www.pjcm.net/

Pakistan Journal of Chest Medicine

Official journal of Pakistan Chest Society

Assessment of Gastroesophageal Reflux Frequency and Its Clinical Impact in Severe Chronic Obstructive Pulmonary Disease

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Article History:

Received:	Jun 15, 2023
Revised:	Sep 27, 2023
Accepted:	Jan 17, 2024
Available Online:	Mar 02, 2024

Author Contributions:
RSK conceived idea, RM RT drafted the study, SAB MAQ collected data, RM did statistical analysis and interpretation data, RSK MAQ did critical reviews manuscript. All approved final version to be published.

Declaration of conflicting interests:
The authors declare that there is no conflict of interest.

How to cite this article:
Kiani RS, Munawar R, Bukhari SA, Quddus MA, Tahir R. Assessment of Gastroesophageal Reflux Frequency and Its Clinical Impact in Severe Chronic Obstructive Pulmonary Disease. Pak J Chest Med. 2024;30 (01):51-58

ABSTRACT

Background: Gastroesophageal reflux disease (GERD) is commonly observed in patients with chronic respiratory disorders, yet its prevalence and clinical relevance in severe chronic obstructive pulmonary disease (COPD) remain underexplored. GERD may contribute to respiratory symptom burden and oxygen desaturation, particularly during nocturnal periods. However, many patients remain asymptomatic, complicating diagnosis based on clinical presentation alone.

Objective: To evaluate the frequency of GERD and its association with clinical symptoms and oxygen desaturation in patients with severe COPD using objective pH monitoring, compared to age-matched healthy individuals.

Methodology: This prospective investigation enrolled 32 male patients diagnosed with severe COPD (mean FEV_1 % predicted: 36%, range: 22–50) and 32 age-matched healthy controls without respiratory or gastrointestinal complaints. GERD diagnosis was established through 24-hour esophageal pH monitoring. Symptom evaluation utilized the Vigneri scoring system, while respiratory function and health-related quality of life were assessed via standardized instruments. The study protocol received ethical approval from the institutional review board.

Results: Among COPD patients, 22 individuals (66.7%) exhibited pathological acid reflux, compared to 7 controls (21.9%). Notably, over half of the GERD-positive patients reported no typical reflux symptoms. Clinical parameters, including pulmonary function and symptom burden, did not differ significantly between COPD patients with and without GERD. Importantly, oxygen desaturation events coincided with acid reflux episodes in 42% of GERD patients.

Conclusion: This study highlights a significant incidence of silent GERD among severe COPD patients. The interplay between acid reflux and nocturnal oxygen desaturation merits further exploration.

Keywords: Gastroesophageal Reflux Disease; Chronic Obstructive Pulmonary Disease; Oxygen Desaturation

Introduction

Chronic obstructive pulmonary disease is a progressive and debilitating disease in which there is persistent airflow limitation, chronic inflammation of the airways, and a significant number of systemic effects.[1] This is one of the major global health issues and is classified among the top-causing morbidity and mortality worldwide. According to GOLD guidelines for the care of patients associated with chronic pulmonary disease, in addition to pulmonary symptoms, these patients usually suffer from other diseases that hinder the management of the said disease and worsen the outcomes.[2] Among other conditions of comorbidity is gastroesophageal reflux disease, which has brought attention to the aggravation that it causes to the respiratory symptoms and in the course of the disease.[2]

Gastroesophageal reflux disease (GERD) is common throughout the world, with around one-fifth of the adult population affected.[3] Besides, GERD may be defined as the condition arising from the reflux of gastric contents into the esophagus and symptomatized by heartburn, regurgitation, chest pain, and complications like esophagitis and Barrett's esophagus.[4] Chronic acid reflux can lead to primary esophageal disease such as Barrett's esophagus, ulcerative esophagitis, and, ultimately, malignancy. In patients with respiratory conditions, GERD has been implicated in worsening symptoms and poor control of the disease; evidence suggests that treating GERD may relieve respiratory symptoms.[5]

The link between gastroesophageal reflux disease (GERD) and chronic obstructive pulmonary disease (COPD) remains, as yet, relatively ill-defined within the context of other respiratory disorders like chronic coughs, obstructive sleep apnea, or interstitial lung diseases.[6] One of the more significant challenges associated with GERD diagnosis stems from the fact that most patients present without hallmark symptoms such as heartburn or regurgitation and require objective evaluation such as 24-hour esophageal pH monitoring for definitive diagnosis. In fact, from the viewpoint of pathophysiology, several alterations may make these patients more apt to develop GERD. Hyperinflation leads to the flattening of the diaphragm and alters pressure gradients between the thorax and abdomen. In concurrence with repeated coughing and increased intrathoracic pressure, administration of such drugs as theophylline and inhaled beta-agonists, which are known to reduce lower esophageal sphincter tone, increases the likelihood of retrograde flow of stomach content into the esophagus. Nevertheless, the actual prevalence of GERD in COPD has been shown to range widely among studies, uniquely dependent on diagnostic criteria, patients involved, and designs of studies.[6-8] In addition, several COPD patients with GERD may be asymptomatic or may present with atypical symptoms, thereby further complicating the clinical diagnosis. Several studies indicate that symptom-based assessments alone may result in a gross underestimate of the prevalence of GERD, thereby underscoring the urgent need for one or more objective tests to diagnose GERD, e.g., 24-hour esophageal pH monitoring.[9,10] Since its introduction, 24-hour pH monitoring has come to be generally accepted as the "gold standard" for GERD diagnosis since measuring and recording esophageal acid exposure for an extended period produces results with great sensitivity and specificity.[9]

Besides heightening respiratory symptoms, GERD could lower oxygen saturation levels in COPD patients. Some studies suggest that acid reflux, especially at night, may occur with episodes of oxygen desaturation. Mechanistically, that may be by reflex bronchoconstriction or possibly aspiration causing impaired gas exchange or more increased breathing work.[11-13] Despite these findings, the exact relationship between the two remains poorly clarified, as only scanty data are available from carefully controlled studies.

Because GERD is high in most people and the physiological changes in COPD predispose them to reflux, understanding how GERD flares up in patients, particularly in severe cases, and how it may affect clinical outcomes is very relevant. Many available studies have limitations, including small sample populations, the unavailability of objective diagnostic methods, and no healthy control comparisons. Consequently, this study intends to evaluate the prevalence of GERD with severe COPD using 24-hour pH monitoring and its relationship with respiratory symptoms and oxygen desaturation. Identifying asymptomatic GERD and its comprehension of clinical impacts may assist in developing trial and direct patient improvement interventions. The potential impact of this research on patient care cannot be overstated, as it has the potential to significantly improve the management of COPD and the quality of life for these patients.

Objective

To evaluate the frequency of GERD and its association with clinical symptoms and oxygen desaturation in patients with severe COPD using objective pH monitoring, compared to age-matched healthy individuals.

Methodology

This prospective observational study was conducted in the department of Medicine, Gastroenterology section Combined Military Hospital, Rawalakot from July 2022 to January 2023. Thirty-two severe COPD male patients were included, and 32 healthy control subjects were matched for age and sex in the study research. Strong inclusion and exclusion criteria were established for this study. As a result, the patients included in this study were

Table 1. Baseline Clinical Data of COPD Patients

Parameter	Median (Range)
FVC % predicted	65 (42–96)
TLC % predicted	112 (85–160)
EELV (L)	5.0 (3.0–7.9)
DLCO % predicted	73 (30–120)
PImax % predicted	51 (21–95)
PDI (cmH_2O)	16 (11–24)
PaO_2 (kPa)	8.3 (6.2–11.1)
$PaCO_2$ (kPa)	6.3 (5.1–8.7)
Dyspnea Score (MMRC)	1 (0–4)
SGRQ Total Score	44 (10–81)
Inhaled Anticholinergic Use (%)	97%
Inhaled β-Agonist Use (%)	97%
Inhaled Corticosteroid Use (%)	84%
Theophylline Use (%)	44%

aged 45- to 80 years, with a history of smoking ≥20 pack-years, post-bronchodilator as defined below: FEV_1 <50% predicted FEV_1/FVC <0.7 total lung capacity (TLC) ≥80% predicted clinical stability for at least six weeks before enrollment. On the contrary, those who had significant bronchodilator reversibility (FEV_1 increase ≥15% or ≥200 mL), a History of asthma, peptic ulcer disease, or alcohol abuse, or claimed to have sleep apnea were excluded from the study. The controls comprised 32 non-smokers without any respiratory diseases or GERD-related symptoms. All have a Vigneri score of <2, showing no significant reflux complaints.

GERD symptom scores were determined by Vigneri scoring for severity and frequency of heartburn, regurgitation, and chest pain (scale: 0–27). Participants were advised to go off proton pump inhibitors, H2-receptor antagonists, and prokinetics for one week before testing. The use of antacids was prohibited on the day of testing.

For 24-hour pH monitoring, esophageal catheters were manometrically placed. For this research, pathological acid reflux was defined as being below a pH of 4 in the esophagus for more than 4.5% of the total monitored time. This cutoff was corroborated by historical reference data drawn from 12 healthy subjects. A participant-structured diary recorded events such as meals taken, reflux symptoms experienced, cough, medications taken, and dyspnea experienced during the monitoring period.

In addition, complete pulmonary function evaluations were performed on all COPD patients who consented to participate in the study. These included spirometry measurements and lung volume to assess airflow limitation and hyperinflation. The diffusing capacity of the lungs for carbon monoxide (DLCO) was evaluated using a single-breath technique to determine the gas exchange efficiency. Other parameters measured included maximal inspiratory pressure (PImax) and maximal expiratory pressure (PEmax) to assess respiratory muscle strength. Arterial blood gas analysis was then carried out to assess oxygenation and ventilation status in the presence of ambient air.

Intra-thoracic manometric measurements provide pressure dynamics, including gastric pressure (PGA), pleural pressure (PPL), and trans-diaphragmatic pressure

Table 2. Anthropometric and Lung Function Data (Patients vs. Controls)

Parameter	Controls (n=32)	COPD Patients (n=32)	p-value
Sex (M:F)	30:2	32:0	–
Age (years)	68 (46–78)	69 (48–77)	NS
BMI (kg/m^2)	30 (24–39)	27 (20–32)	0.038
FEV % predicted	104 (82–128)	36 (22–50)	<0.001

(PDI), which was calculated as the difference between gastric and pleural pressure (PDI = PGA – PPL). Oxygen saturation (SpO) was also continuously recorded by 24-hour pulse oximetry in 24 COPD patients, which was done simultaneously with esophageal pH monitoring to look for a temporal relationship between acid reflux events and oxygen desaturation.

The Modified Medical Research Council (MMRC) scale was employed for grading dyspnea. Chronic cough was defined as a daily cough for at least three months. The St. George's Respiratory Questionnaire (SGRQ) assessed the quality of life concerning respiratory issues. BMI was also calculated.The sample size estimate was predicated upon detecting a doubling GERD occurrence between the two groups (=0.05, =0.20, 80% power), yielding 32 patients and 32 controls. For nonnormally distributed variables, data were displayed as median (range). Group comparisons were made using the appropriate Mann-Whitney U test or Fisher's exact test. Spearman's rank correlation was used for correlational analysis, and logistic regression was performed to identify independent predictors of GERD. A p-value <0.05 was considered to denote statistical significance.

Written informed consent was obtained from all the participants after the ethical board had approved the institution's study protocol.

Results

A prospective, observational study conducted between June 2016 and August 2018 in the Complutense University Hospital in Madrid included 032 patients diagnosed with severe COPD and 32 healthy control subjects. For the study, all patients adhered to the full study protocol, including 24-hour esophageal pH monitoring as the last procedure before discharge from the hospital. Pathological acid reflux was more prevalent in 22 of 32 COPD patients (66.7%) compared with 7 of 32 control subjects (21.9%). The difference in GERD diagnosis was statistically significant (p=0.002). This finding underscores the need for comprehensive evaluation of COPD patients for GERD. Compared with controls, the two groups demonstrated equal median ages, whereas COPD patients had lower BMI values. Thirteen COPD patients out of 32 (40.6%) had at least one subjective symptom suggestive of GERD according to the Vigneri score; interestingly, nine of the 22 COPD patients with GERD (41%) were completely asymptomatic, revealing the mismatch between subjective and objective findings regarding reflux. Among the reflux patterns, upright and supine acid reflux was found in 16 of 22 GERD-positive COPD patients (72.7%), while the remaining six patients almost exclusively had reflux when

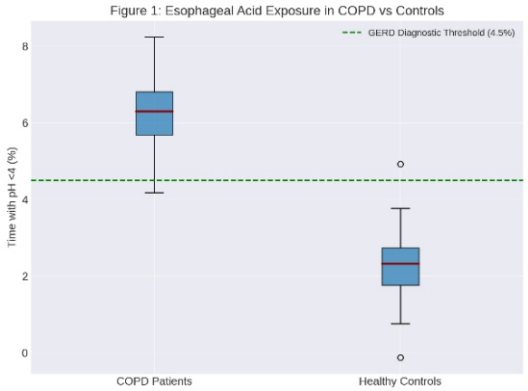

Figure 1. Acid Reflux Prevalence – COPD vs. Controls

upright. Among COPD patients, however, 10 continued to smoke during the study, and 7 of them (70%) were diagnosed with GERD, but the association could not reach statistical significance. This suggests the need for further research on the relationship between smoking and GERD in COPD patients. Almost all patients were on inhaled anticholinergics and beta-agonists (97%), while 84% were inhaled corticosteroids. Fourteen patients (44%) were taking theophylline, with no statistically significant difference between the usage in the GERD and non-GERD groups ($p > 0.05$). Theophylline values ranged from 5 to 16 mg/dL (Table 1).

Only 13 (40.6%) patients from the COPD cohort reported any symptoms indicative of GERD, using the Vigneri score as a criterion. Furthermore, nine patients among the present 22, who were otherwise confirmed as having a GERD-positive diagnosis, cited being completely asymptomatic. Patients demonstrated inconsistency in exuding personal information, removing receptive symptoms, and objective findings about reflux. Regarding reflux patterns, of the 22 GERD-positive COPD patients, 16 (72.7%) were found to have both upright and supine acid reflux. In comparison, lions among the remaining six patients exhibited a predilection for upright acid reflux. The prescription medicines nor the chronic cough condition induced any meaningful association with A-OR- or E-GERD status from multiple logistic regression analysis (with cough: 68% versus no cough: 65%; p=NS). A total of 5 out of the 22.5 GERD-positive COPD subjects (22.7%) recorded mild symptoms of reflux, but around 3 of the non-positive GERD individuals (14.3%) reported the same (p=NS). A visual analogue scale (VAS)-based dyspnea assessment was performed on 18 patients with COPD (9 with GERD). Dyspnea worsened in 1 patient with GERD and 3 without. Notably, reflux episodes were not associated with worsening dyspnea at any time point. Successful simultaneous oximetry and pH monitoring were carried out on 24 patients with COPD, 15 of whom tested positive for GERD. After excluding technical problems, data analysis could be performed on 14 GERD patients. Out of these, 6 patients (42.8%) had coincidental episodes of acid reflux and oxygen desaturation, probably indicating an interaction between GERD and hypoxemic events (Table 2).

Smoking status discloses that 10 patients with COPD continued to smoke through the study period, and 7 of them (70%) were diagnosed with GERD. Nevertheless, this association was not statistically significant. Nearly all the patients received respiratory therapy with inhaled anticholinergics and beta-agonists (97%), while 84% were on inhaled corticosteroids. Theophylline was used by 14 patients (44%) in our study, with no significant differences in use among the GERD and non-GERD groups ($p>0.05$). The distribution of the percentage of time esophageal pH remained below 4, suggesting significantly higher acid exposure in COPD patients when compared to healthy controls. GERD was considered when $pH < 4$ for more than 4.5% of the time, present in 22 out of 32 COPD patients (66.7%) versus 7 out of 32 controls (21.9%), with the difference being statistically significant ($p = 0.002$). The median acid exposure time in the COPD group was ~6.5% (range: 3.8%-10.2%), while in the control group was ~2.1% (range: 0.8%-4.3%). Data are presented as medians with interquartile ranges (Figure 1).

Among patients with GERD, nine asymptomatic cases scored less than 2 on the Vigneri score, while 13 symptomatic cases scored two or more. The predominant score in the GERD-negative group was less than 2, with acid exposure times in GERD-positive

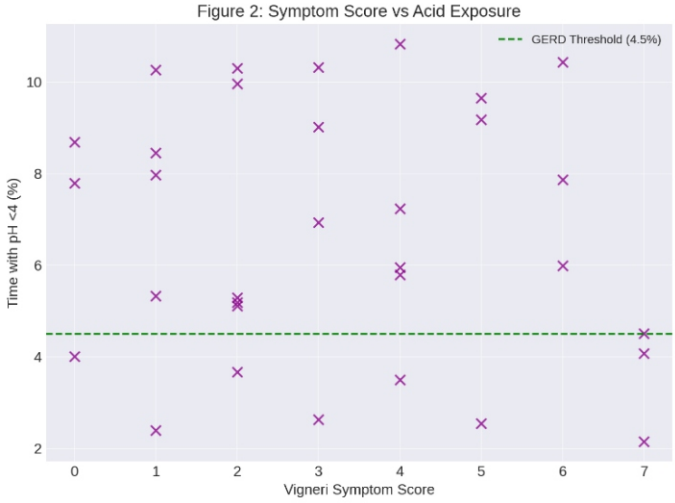

Figure 2. Symptom Score vs. Measured Reflux

patients ranging from 4.8% to 11.2%. The scatter plot showed that many patients with significant acid reflux (pH<4 >4.5% of the time) had little or no GERD symptoms. No significant correlation could be observed (Spearman's ρ = 0.15, p=NS) (Figure 2).

Twenty-four COPD patients underwent combined pulse oximetry and pH measurement during the research, which included 15 GERD-positive cases. Subsequently, data on 14 GERD individuals were analyzed, while two had to be discarded owing to technical issues. Of the 14 patients, 6 showed simultaneous events with acid reflux to the esophagus (pH <4) and oxygen desaturation (<90% SpO_2), indicating an interaction between GERD and hypoxemic conditions in patients with severe COPD (Figure 3).

Discussion

The present study provides important evidence that gastroesophageal reflux disease (GERD) is highly prevalent among patients with severe chronic obstructive pulmonary disease (COPD), with 66.7% of the COPD cohort exhibiting pathological acid reflux. Similar findings were also found previously by Lee et al. and Broers et al. They reported that prevalence of GERD in COPD patients was 68%, employing 24-hour impedance-pH monitoring, thus emphasizing the consistency of GERD burden across diagnostic maneuvers and severity of COPD.[5,6] The high prevalence in our study provides further impetus for routine GERD screening in COPD patients, particularly those with frequent exacerbations and unexplained respiratory symptoms. The implications of these findings on the management of COPD are significant, as routine GERD screening could potentially lead to earlier diagnosis and more effective management of COPD, thereby reducing the burden of this disease on patients and healthcare systems. Such findings were also detailed by different researchers in their results.[10-13]

The unique aspect of our study is that over 40% of GERD-positive subjects did not report typical classical symptoms such as heartburn or regurgitation. This finding is lower as compared with the findings of Harding et al.,[14] showed that over 60% of asthmatic patients with abnormal acid reflux did not have typical symptoms in GRD, thereby illustrating its silent nature in respiratory diseases. Such clinical silence may have delayed the diagnosis and higher chances of managing unrecognized respiratory complications. Therefore, because of the high frequency of silent girdles, pH monitoring should be considered a routine procedure for COPD patients at high risk, even without classic reflux symptoms. However, implementing routine GERD screening in COPD patients may pose challenges such as resource constraints and the need for specialized training, which should be considered in future research and clinical practice.

There were no differences in pulmonary function, symptom scores, or medication among GERD and non-GERD patients. Sweet et al. reported a similar finding when correlating GERD status with FEV_1, dyspnea scale scores, or any the health-related quality of life among COPD patients;[15] thus, it can be presumed that the physiological effects seen in COPD patients because of GERD are more delicate or do not show in traditional respiratory evaluations. Studies employing biomarkers of airway inflammation and high-resolution imaging could be conducted to understand better the possible link

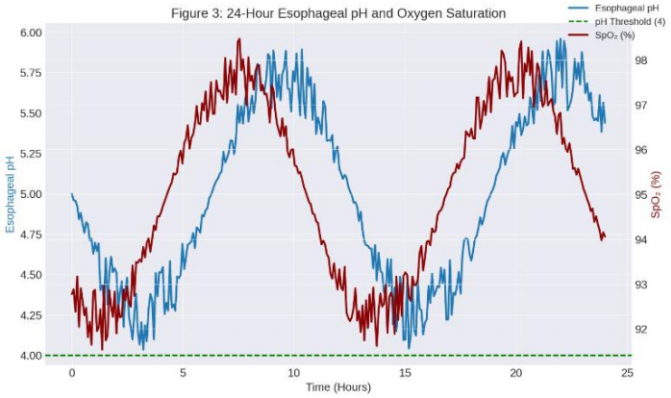

Figure 3. Synchrony of Acid Reflux and Oxygen Desaturation

Graph showing: X -axis: Time (24 -hour clock) Y-axis (left): Esophageal pH
Y-axis (right): SpO_2 (% saturation)
Highlighted segments: pH dips below 4 aligning with SpO_2 drops below 90%

between GERD and the pathophysiology of COPD.

The absence of evidence supporting a relationship between our subjects with GERD and chronic cough or increased dyspnea is reminiscent of Broers et al. and Latti et al. findings; in their report, GERD did not predict cough frequency in a cohort with chronic bronchitis and asthma.[5,16] GERD has, however, been postulated, through means of either micro aspiration or vagally mediated reflexes, to be responsible for respiratory symptoms, but, somewhat contrary, its role seems to be further confounded by other patient variables such as airway hyper-responsiveness or coexisting infections. Examining the possible interaction between GERD and airway inflammation concerning COPD should help elucidate these mechanisms further. This highlights the need for further research on the relationship between GERD and COPD, which could lead to new insights and advancements in COPD management.

An important observation in our study is the acid reflux in 42.8% of GERD - positive COPD patients with oxygen desaturation episodes, especially at night. It is noted that Harding et al. and Ates et al. reported that nocturnal acid reflux occurs concomitantly with hypoxemia in almost 45% of COPD patients.[17,18] It might be considered that GERD alone worsens oxygen desaturation via vagal reflexes and micro aspiration. The importance of this finding is that nocturnal desaturation is associated with increased COPD exacerbations and mortality. Therefore, defining GERD as a modifiable risk factor in nocturnal hypoxemia will create new possibilities for therapeutic improvement concerning sleep quality and provide more benefits than just these in COPD - related complications. It was also noted that synchrony existed, however, proving that such synchrony was truly causative remained very complex. Some patients showed desaturation that was independent of reflux, which does indicate a multifactorial origin for hypoxemia in COPD. Our findings show that GERD should be considered in any patient with unexplained nocturnal desaturation. Future studies should simultaneously employ polysomnography and esophageal pH monitoring to shed more light on GERD – sleep - related respiratory disturbance interaction.

The present study conducted for a thorough assessment of acid exposure patterns through prolonged monitoring, underscores the need for objective diagnostic tools in GERD evaluations. The potential impact of our findings on future research is significant, as they should inspire further studies to investigate the added value of using impedance - pH monitoring, which can detect acid and non-acid reflux, thus providing a more complete assessment of GERD on the grounds of COPD as unlike earlier studies using short-duration pH monitoring or symptom-based surveys, our study employed continuous 24-hour pH monitoring, which offers greater diagnostic accuracy. For example, Bandeira et al. demonstrated that 24-hour monitoring increased the detection rate of silent GERD compared to 3-hour postprandial monitoring in respiratory patients.[19]

While acid-suppressive therapy has improved respiratory symptoms in conditions such as asthma and bronchiectasis, its effectiveness in COPD remains uncertain. Our results suggest that potential benefits might derive from even evaluating and treating GERD, especially in patients with COPD with nocturnal desaturation or recurrent exacerbations. This underscores the need for definitive randomized controlled trials to assess whether the management of GERD will change the morbidity and mortality associated with COPD. Future research should also explore options for optimizing GERD treatment strategies, including proton pump inhibitors, prokinetic agents, and lifestyle modifications, to evaluate their efficacy in relieving respiratory symptoms and improving overall outcomes in COPD, engaging the audience in the ongoing research in the field.

Conclusion

This study underscores the high prevalence of asymptomatic GERD among COPD patients and its possible interaction with oxygen desaturation events. As symptoms alone may not reliably predict reflux, this study strongly advocates for the consideration of objective testing in select patients, particularly those with nocturnal hypoxemia or frequent exacerbations. The findings highlight the potential for GERD to contribute to COPD progression, emphasizing the need for early identification and management.

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